

A Study of the Formation of Pyrimidines

BY THE USE OF

Nitromalonic Aldehyde

BY

Harvey Clayton Brill

1911



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A Study of the Formation of Pyrimidines

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Nitromalonic Aldehyde

A Thesis

Submitted to the Faculty

OF THE

Department of Literature, Science and the Arts

OF THE

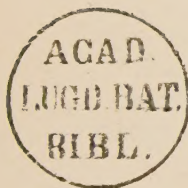
University of Michigan

In Partial Fulfillment of the Requirements for the
Degree of Doctor of Philosophy

BY

Harvey Clayton Brill

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It is with deep gratitude that acknowledgement is hereby made to Professor William J. Hale for the valuable suggestions and constant interest which he has taken in the direction of this research.

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Theoretical Considerations

In a paper published by Hill and Torrey¹ in 1899 it was shown that both aldehyde groups of sodium nitromalonic aldehyde may be jointly involved in certain condensations which result in the formation of closed ring bodies. Condensations with various ketones and ketonic acids were described by these authors, and again by Soch and Oenslager² in a paper published in 1900. Hill and Torrey proved that with acetone the condensation took place by involving both of the methyl groups conjointly and resulted in the formation of the benzene ring. * An intermediate product, a derivative of dihydrobenzene is first formed, but by the addition and subsequent elimination of water this dihydrobenzene derivative passes into paranitrophenol. Similar condensation products resulted from the action of sodium nitromalonic aldehyde on certain derivatives of acetone. Soch and Oenslager described the various compounds obtained by the action of methyl-ethyl ketone, dibenzyl ketone, acetoacetic ester, laevulinic acid, and acetone dicarboxylic acid on this aldehyde. Hill and Hale³ have shown that a condensation with benzyl-methyl ketone gives a derivative of phenylbenzene, a 5-nitro-2-hydroxydiphenyl.

It was also proved that the aldehyde groups of nitromalonic aldehyde can react with amino groups, giving with aniline, for instance, either a monanil or a dianil. With phenylhydrazine the reaction ran similarly, but the compounds were less stable, and on warming readily underwent decomposition into 1-phenyl-4-nitropyrazole, $C_7H_9N_3O_2$.

From these facts it was thought that there might be a possibility of condensing the two aldehyde groups of nitromalonic aldehyde conjointly with the two amino groups of α -diamino compounds and thus form a 6-ring body containing two nitrogen atoms in the meta position, *i. e.*, a pyrimidine. Pinner⁴ in his synthesis of pyrimidines has accomplished this by making use of vari-

¹ Amer. Chem. Jour., 22, 89 (1899).

² Amer. Chem. Jour., 24, 1 (1900).

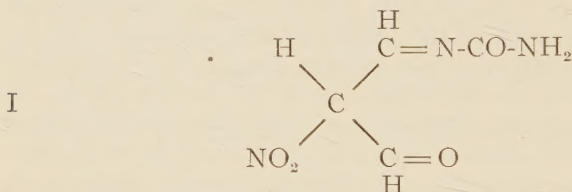
³ Amer. Chem. Jour., 33, 1 (1905).

⁴ Ber. d. deutsch. Chem. Ges., 23, 161 (1890). Ber. d. deutsch. Chem., 26, 2125 (1893).

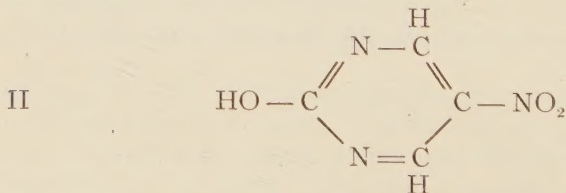
ous amidines with β -diketones and ketonic acids. The reactions ran smoothly and with very good yields.

The study of the action of sodium nitromalonic aldehyde upon urea, and variously substituted ureas, was undertaken in the fall of 1908 in this laboratory.

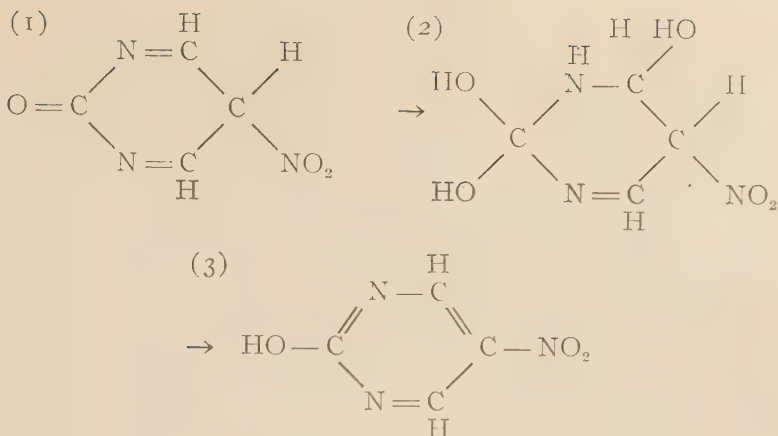
The reaction with urea in aqueous solution in the presence of sodium hydroxide or piperidine, as a condensing agent, was first studied. On allowing the solution to stand for some time at room temperature, a deep red color developed from the original yellow solution. At the end of twenty-four hours, or longer, the solution was acidified with sulphuric acid (1-5) and a light pink, semi-crystalline precipitate was obtained. The precipitate is not a ring body but a monoureide of nitromalonic aldehyde,



indicating that a condensation must have taken place with but one aldehyde group. After filtering off this precipitate and allowing the mother-liquor to stand for some time another precipitate appeared. This product was plate-like in form, possessed a deeper yellow color and melted at 203.5° when purified. Here we had the ring body where the condensation involved both of the amino groups of the urea. The product is β -nitro- μ -hydroxypyrimidine (II).

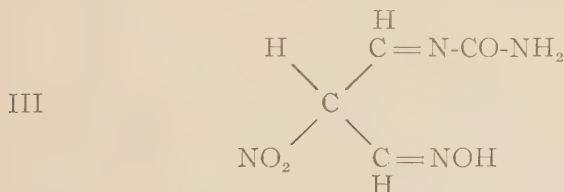


We can assume, as Hill and Torrey (see page 1), that a dihydro compound (1) was first formed by the joint condensation of the two amino groups with the two aldehyde groups, and that this by the addition of water (2) and later splitting off of water (3) gave the pyrimidine formulated below.



This probable formation of a dihydropyrimidine as the intermediate product in passing from the monoureide to the pyrimidine has a possible substantiation in the work of P. N. Evans⁵ and A. and C. Combes.⁶

The constitution of the monoureide of nitromalonic aldehyde has been determined by the synthesis and analysis of the compounds following. The monoxime monoureide of nitromalonic aldehyde was made by the method of V. Meyer and Janny.⁷



This indicates the presence of a free aldehyde group in the monoureide.

In the attempt to form the monanil compound by the addition of aniline to an alcoholic solution of the monoureide, a monanil of nitromalonic aldehyde was obtained each time with the splitting off of urea. This monanil is identical with that of Hill and Tor-

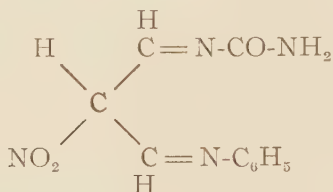
⁵ Jour. f. pr. Chem. (2) 48, 489 (1893).

⁶ Bull. Soc. Chim. Paris, Series 3, 7, 788 (1892). These investigators assumed a structure of such type for the condensation product obtained from urea and acetylacetone.

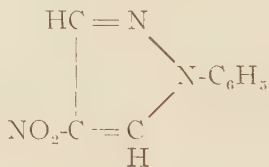
⁷ Ber. d. deutsch. Chem. Ges., 15, 1324 (1882).

rey made by the action of aniline hydrochloride on sodium nitromalonic aldehyde itself. A determination of the urea showed that one molecule was split off. To obtain the monanil monoureide of nitromalonic aldehyde (IV), the monanil of nitromalonic aldehyde was made and suspended in alcohol in the presence of the theoretical amount of urea. Into this alcoholic solution gaseous hydrogen chloride was passed until the whole had passed into solution and the color had become a deep red. The compound precipitated out in long, slender, red needles on cooling.

IV

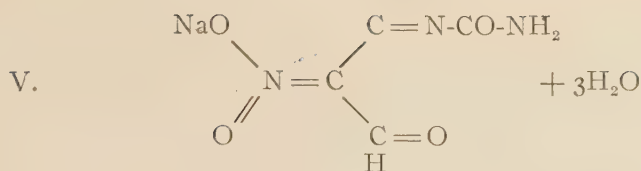


When phenylhydrazine was added to the monoureide of nitromalonic aldehyde in a solution of alcohol and glacial acetic acid, urea was split off in the same way as on the addition of aniline to the monoureide. The phenylhydrazone was probably first formed but was so-unstable that it could not be isolated even in the cold, and changed to the 1-phenyl-4-nitropyrazole with the splitting off of urea:

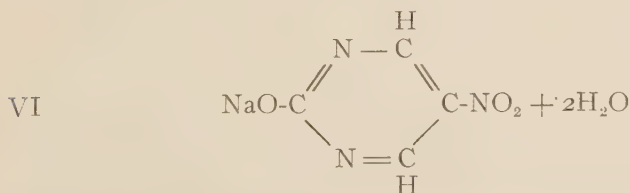


We were unable to form a phenylhydrazone of the monoureide of nitromalonic aldehyde. The method of first forming the phenylhydrazone of nitromalonic aldehyde suggested itself but its ready transformation into 1-phenyl-4-nitropyrazole precluded any successful attempts in this direction.

The sodium salt of the monoureide was made and analyzed according to formula (V), indicating therefore the presence of one hydrogen atom replaceable by metals. The parent substance, with its one free aldehyde group is shown therefore to accord with formula I.

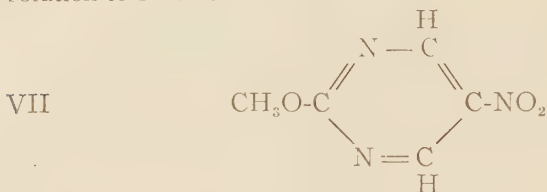


Various attempts were made to close the ring of the ureide compound by the elimination of one molecule of water to the formation of the β -nitro- μ -hydroxypyrimidine, but with no uniformly successful results. When the monoureide of nitromalonic aldehyde, as first prepared, is allowed to remain in suspension in the mother liquor, a large portion of it was found to have undergone a further condensation into the pyrimidine in the course of a few days. Of course a mixture of the monoureide and the pyrimidine is obtained under these circumstances, so that the final product gives no fixed melting point. The yield of the pyrimidine was increased by warming the solution to about 40° just before adding the sulphuric acid. By warming the monoureide on the steam bath with such dehydrating agents as sulphuric acid, acetic anhydride and hydrogen chloride, anhydrous sodium acetate or phosphorus pentoxide in an acetic anhydride solution, a further condensation to the ring body was obtained with somewhat varying results. Some of these trials were made at higher temperatures and pressures but deep-seated decomposition always took place; for example, when the monoureide in hydrochloric acid (1-5) is heated in a sealed tube at 100° ammonium chloride was obtained. A similar decomposition takes place when the ureide is heated in a sealed tube with acetic anhydride. A condensation of the monoureide to the pyrimidine may be effected when its alcoholic solution is warmed with sodium alcoholate under a reflux condenser for two to three hours. The sodium salt of the pyrimidine (VI) was formed in this case, but the yield is only fair.



The presence of only one replaceable hydrogen was confirmed by the formation of a mono-silver salt through the addition of silver nitrate to the clear aqueous solution of the ammonium salt.

The methyl ether (VII) of this pyrimidine was made by warming the sodium salt, prepared as given above, with methyl iodide in methyl alcoholic solution for three hours under a reflux condenser. The methyl alcohol solution was evaporated to dryness and the residue extracted with benzene. The ether is soluble in the benzene and crystallizes out on evaporating the benzene solution to small volume.



In order to determine the position of the methoxyl group an estimation according to Zeisel's⁸ method was carried out. The group split off at a low temperature, hence it was concluded that it is attached to the carbon rather than to the nitrogen as is the case in many of the pyrimidines. This confirms the above formula.

Our previous work has shown that the pyrimidine formed by the action of nitromalonic aldehyde on urea has a hydroxyl group (and a methoxyl group, when the ether is concerned) which is attached to the carbon. This proves that our structural formula is correct. We also learned that the urea condenses slowly with the aldehyde to give the monoureide, involving but one aldehyde group and that later the pyrimidine is formed by the condensation of the second aldehyde group with the second amino group of the urea.

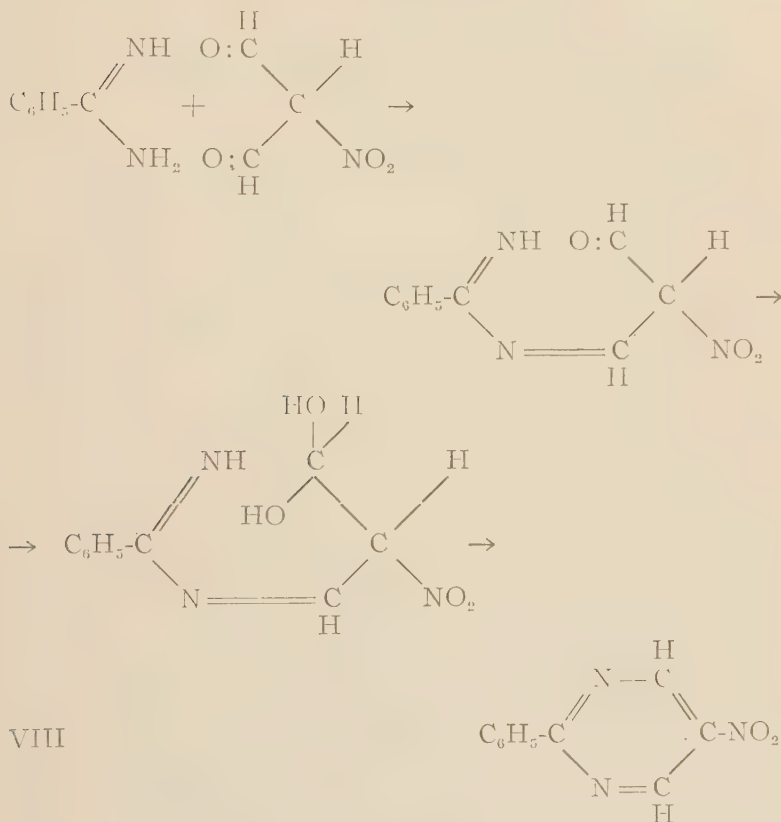
As Pinner's yields of the pyrimidines by the action of amidines on β -ketonic esters were almost quantitative, it was decided to try the action of benzamidine on this aldehyde in order to ascertain what influence the presence of the imino group would have upon the rate of this condensation with nitromalonic aldehyde.

Equimolecular quantities of benzamidine hydrochloride and nitromalonic aldehyde when brought together in aqueous solution formed a white, crystalline precipitate almost immediately. This action proceeds without the presence of a condensing agent, though enough sodium hydroxide was usually added to neutralize the hydrochloride. An almost quantitative yield was obtained.

⁸ Monat. f. Chem. 6, 989 (1885). Monat. f. Chem. 7, 406 (1886). Ber. d. deutsch. Chem. Ges., 27, 369 (1894). Ber. d. deutsch. Chem. Ges., 35, 3221 (1902).

The compound gave no test for sodium and was not soluble in sodium hydroxide, therefore a replaceable hydrogen atom cannot be present. It did not react with phenylhydrazine or aniline, hence both aldehyde groups must have been involved with the amino and imino groups to the formation of β -nitro- μ -phenylpyrimidine. Analysis confirmed the above conclusion.

The theory of the formation is as follows :



An intermediate body is no doubt first formed where only one aldehyde group has condensed with the amino group, then by the addition of water to the free aldehyde group and the subsequent splitting off of water and sodium hydroxide the pyrimidine (VIII) is formed. Thus the pyrimidine is obtained without the addition of acid to set it free from the sodium salt. The sodium is split off as sodium hydroxide.

It has been pointed out that nitromalonic aldehyde condenses very slowly with urea in the presence of a condensing agent. With benzamidine, on the other hand, it condenses almost immediately in the absence of a condensing agent to the closed ring body,—the β -nitro- μ -phenylpyrimidine. An intermediate body; a mono-ureide of nitromalonic aldehyde is isolated by the condensation with urea; such an intermediate product cannot be isolated from the condensation with benzamidine.

The speed of the reaction with benzamidine, contrasted with the slower rate of the action with urea, indicates that the imino group may have an influence on the velocity and yield of the reaction.

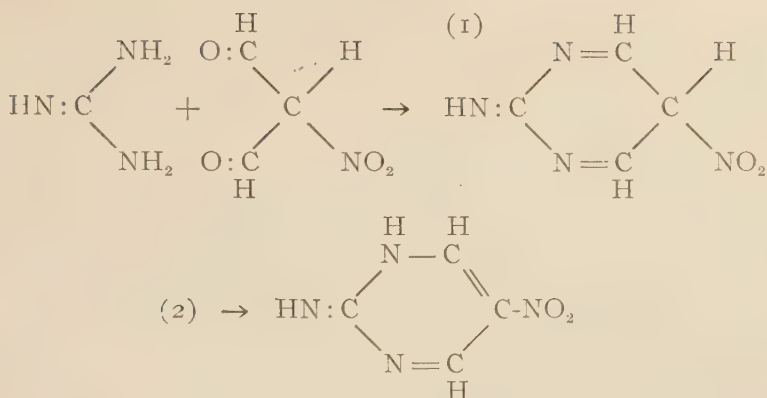
Pinner's quantitative yields of pyrimidines from the action of β -ketones on amidines made this theory appear so plausible that it was determined to make further experiments leading to its confirmation.

Guanidine was selected as the substance offering the possibilities sought. In this compound two amino groups and one imino group are attached to the same central carbon atom, and consequently the tendency for any one or two of these groups to enter into a ring condensation may be studied.

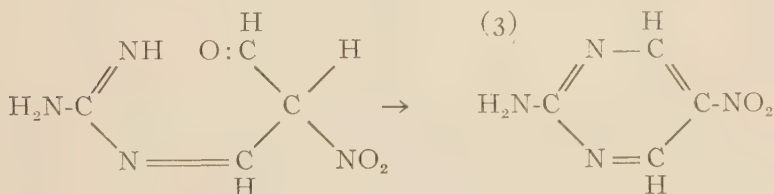
Should these two amino groups enter readily into a reaction of this type, they must be involved in the condensation either simultaneously or one after the other; but, on the other hand, if one amino group and the imino group offer the more reactive combination with nitromalonic aldehyde, as we have believed, these two alone should be involved, leaving the second amino group free. The reaction, in accordance with this theory, should proceed smoothly to the formation of a pyrimidine.

Thus when guanidine and nitromalonic aldehyde were mixed in aqueous solution, the mixture immediately became red and a white, needle-like, crystalline precipitate formed, even in the absence of a condensing agent. The yield of this product may be made almost quantitative by the use of piperidine as a condensing agent. Thus we find that the rate and yield are what we should expect from theoretical considerations, but it remains to be shown whether or not the condensation has taken place as predicted, *i. e.*, whether one amino group and the imino group, in preference to the two amino groups, have entered jointly into the condensation with the two aldehyde groups of nitromalonic aldehyde.

If the two amino groups reacted with the aldehyde groups we should have either (1), or (2) by the addition and splitting off of water.



If an amino and the imino group are involved we should have



If (1) or (2) is correct the imino group is present and can be tested for, but if (3) is the correct structural formula the presence of the amino group may easily be shown. The course of the reaction can be determined by obtaining proof that either the imino or an amino group is present. To learn the structure the following reactions were carried out:

a. HOFFMAN'S CARBYLAMINE TEST.⁹

The compound warmed with alcoholic potash and chloroform gave the characteristic odor of a carbylamine. This is proof of the presence of the amino group.

b. HINSBERG'S TEST.¹⁰

With benzene sulphochloride a clear solution was obtained on the addition of potassium hydroxide. If the imino group were present an oily benzene sulpho-derivative would have been formed.

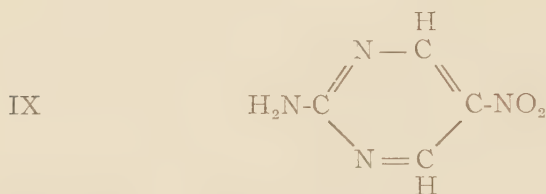
⁹ Ber. d. Chem. Ges., 3, 767 (1870).

¹⁰ Ber. d. deutsch. Chem. Ges., 23, 2962 (1890). Ber. d. deutsch. Chem. Ges., 23, 3198 (1890).

The amino group forms a soluble salt, since its hydrogen is made negative enough by the close proximity of the sulpho group to be replaced by metals.

c. LIEBERMAN'S NITROSAMINE TEST.

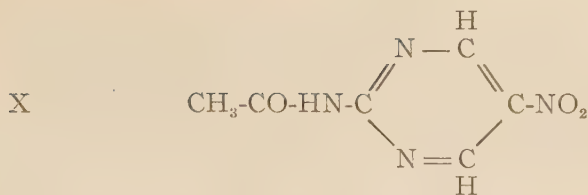
This test gave negative results, indicating the absence of an imino group. These results prove beyond a doubt that an amino and imino group have reacted with the two aldehyde groups leaving a free amino group and that they, rather than the two amino radicals, are the more reactive combination. Our formula for the pyrimidine is, therefore, that of a β -nitro- μ -aminopyrimidine:



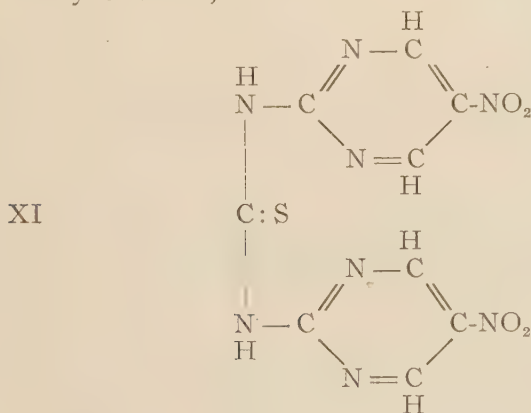
If the structural formula above is correct a hydrochloride should be possible of formation. The aminopyrimidine was warmed with concentrated hydrochloric acid. The solution became clear on warming but the original body came out when the solution cooled. Dry hydrogen chloride was passed into an alcoholic solution and into an acetone solution of the pyrimidine but without success in either case. This failure to form the hydrochloride is probably caused by the negative character given to the compound by the presence of the nitro group in the ring, though it may be due to the breaking up of the hydrochloride when isolated from the solution, *i. e.*, it may exist to some extent in solution because of the large amount of hydrogen chloride present, but be so unstable that it undergoes decomposition when removed from the presence of the free acid; or again it may not be formed under the conditions chosen for the experiment.

To confirm our conclusions concerning the structure of this compound some of its derivatives were made and studied.

The acetyl derivative (X) was obtained by warming the β -nitro- μ -aminopyrimidine with acetic anhydride in the presence of anhydrous sodium acetate. This compound can be made in the absence of anhydrous sodium acetate but the yield is smaller. It is hydrolized to the original β -nitro- μ -aminopyrimidine by warming with water.



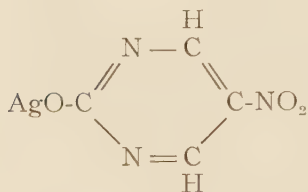
Upon suspending this aminopyrimidine in carbon disulphide¹¹ and warming in the presence of a small amount of potassium hydroxide, a yellow, oily mass was thrown down. This mass appears as a yellow plate-like, crystalline body, characteristic of thio-compounds, when digested with alcohol. This is an $\alpha\alpha'$ substituted thio-urea (XI), or a symmetrical β, β' -dinitro- μ, μ' -dipyrimidyl thio-urea,



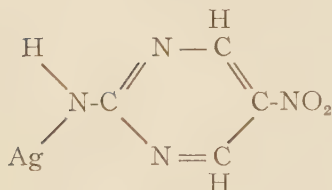
The β -nitro- μ -aminopyrimidine has no hydrogen atom replaceable by metals. When boiled with weak alkali it went into solution in the hot liquid giving only a faint yellow tinge to the liquid, but on cooling the original pyrimidine was thrown down. If, however, the alkali is highly concentrated and the warming continued for some time, the odor of ammonia may be detected and the solution made to acquire a deep red color. (The alkali salts of β -nitro- μ -hydroxypyrimidine are deep red.) A concentrated solution of ammonium hydroxide will effect this change slowly. To determine if the hydroxy-pyrimidine was formed the excess of ammonia was driven off and the silver salt prepared by adding silver nitrate to the solution. The red-brown silver salt

¹¹ Ann. d. Chem. (Liebig) 70, 144 (1849).

came down immediately. It is only slightly soluble in water and resembles the silver salt of the hydroxypyrimidine in all particulars. A nitrogen determination gave the theoretical amount of nitrogen for the hydroxypyrimidine. As can be seen by contrasting the formulae of the two pyrimidines, a nitrogen determination of either is sufficient to distinguish it conclusively from the other, viz.:



M. W. = 248
% nitrogen = 16.93



M. W. = 247
% nitrogen = 22.67

The methyl ether was made by warming the silver salt under the reflux condenser for some time with methyl iodide. The product formed gave the same melting point as the β -nitro- μ -methoxypyrimidine.

Hydrochloric acid added to this silver salt formed a precipitate of silver chloride. If this, as our previous experiments would indicate, is the salt of a phenol, then upon the addition of hydrochloric acid we should have the original β -nitro- μ -hydroxypyrimidine formed, which previously was made by the condensation of urea with nitromalonic aldehyde. By following the above procedure we were able to secure small amounts of this β -nitro- μ -hydroxypyrimidine when the acid solution was evaporated to small volume.

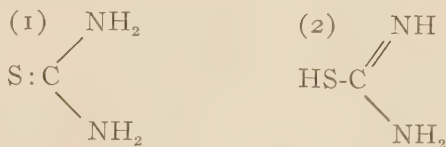
These experiments proved conclusively that guanidine condenses with nitromalonic aldehyde to form an analogous compound to that formed by the action of urea with this aldehyde, that one amino group remains free and that an hydroxyl group may be substituted for this amino group by warming with alkali.

As a result, we are led to the conclusion that an amino group taken in connection with an imino group, as typified in benzamidine or guanidine, offers a more reactive setting for combination

with nitromalonic aldehyde than does the α -diamino arrangement in urea.

These results, as just given, may well be applied to a study of thio-urea when brought into condensation with nitromalonic aldehyde.

There are two formulae given for thio-urea, one (1) where we have the diamino grouping such as we have in urea, and a second (2), or the pseudo form, in which we have instead of the α -diamino grouping, an amino group in the same relative position with an imino group.



From a study of the oxidation of thio-urea in acid solution and its action with acetyl chloride Ad. Claus¹² was led to the belief that this urea existed primarily in a pseudo form and contained therefore the mercapto group.

Johnson and Hill,¹³ in a recent study of the action of thio-urea on the esters of allylmalonic acid and some alkyl substituted allylmalonic esters, found that in certain cases thio-urea reacted in such a way as to indicate the presence of a mercapto group, and of course here the imino and amino groups must be present in just such an arrangement as we find in guanidine and benzamidine.

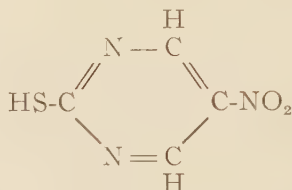
Dixon and Hawthorne,¹³ investigating the action of acetyl chloride and benzyl chloride on thio-urea, found that an unstable acetyl derivative was first formed, which readily underwent isomerism to a more stable form when heated with dilute alkali or, in some cases, upon warming without the presence of the alkali. They came to the conclusion that the unstable compound was the acetyl derivative where the acetyl radicle was attached to the sulphur atom. By heating, the labile acetyl radicle shifts to the amino group forming a more stable isomer of the sulpho-derivative. If such is true thio-urea must in these reactions exist in the pseudo form and have an amino and an imino group attached to the same carbon.

¹² Jour. pr. Chem. (2) 47, 135 (1893).

¹³ Amer. Chem. Jour. 45, 356 (1911).

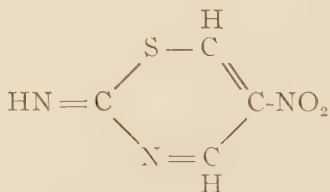
¹⁴ Jour. Chem. Soc. (London) 91, 122 (1907).

With the imino grouping present in thio-urea we should expect, from our theory, that its condensation with nitromalonic aldehyde would proceed with ease to the formation of β -nitro- μ -mercaptopyrimidine.



The action with benzamidine, guanidine and urea proceeded in just this manner.

In the work of Johnson and Hill, previously cited, it was found that the mercapto group took part in the condensation forming a ring body containing a sulphur atom, a so-called hexathiazole. The same possibility is present in this study and would naturally lead to the formation of a β -nitro- μ -iminometathiazine.

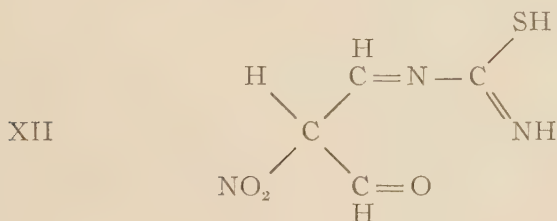


Whether this compound or the pyrimidine is formed depends entirely upon which of two possibilities is the more reactive combination towards the aldehyde groups; either the mercapto and the amino groups, or, on the other hand, the imino and the amino groups.

Thio-urea and sodium nitromalonic aldehyde, when brought together in aqueous solution, underwent a speedy reaction, as was shown by the change in color of the solution. If piperidine is used as a condensing agent, a light yellow product of needle-like structure was thrown down in the alkaline solution, the yield dependent upon the quantity of piperidine used. When diethylamine or sodium hydroxide were used this compound was not formed. On addition of dilute acid to these solutions a deep yellow, semi-crystalline body was precipitated. The melting point in this case was somewhat higher than that of the first compound

mentioned. This same substance may be obtained by the addition of acid to the mother liquor from the piperidine condensation.

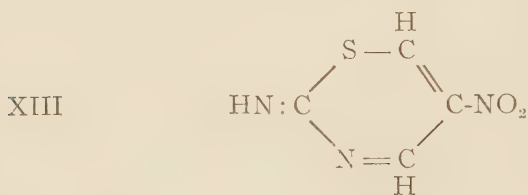
For a time it was thought that this was the pyrimidine, but later it was found to react with phenylhydrazine or with aniline to form the hydrazone or the anil respectively, thus proving the presence of the aldehyde group. Hence the condensation must have taken place with only one aldehyde group in a manner similar to the action of urea with nitromalonic aldehyde and with the production of a monothio-ureide of nitromalonic aldehyde (XII).



If this compound is suspended in alcohol, in which it is only very slightly soluble, and piperidine added, immediately upon going into solution, the first body, just mentioned, is precipitated. This may be a piperidine salt or a new product formed by the condensation of the remaining aldehyde with either the imino or mercapto group. That it is not the piperidine salt was proved by the fact that the monothio-ureide derivative was not liberated upon the addition of sodium hydroxide. Sodium hydroxide should displace the piperidine since it is the stronger base. It did not go into solution when warmed with sodium hydroxide, except on long warming; and then the original sodium nitromalonic aldehyde was found in solution with its decomposition products. Were the mercapto group present a sodium salt would be readily formed and would doubtless be soluble in water, therefore this indicates the absence of the mercapto radicle. A substantial proof that the mercapto group is no longer present may be found when this compound is warmed with a basic solution of lead acetate or mercuric oxide. In both of these cases there is no desulphurization of the body but the original body was again obtained after warming for several hours under a reflux. This indicates that the sulphur is placed between two carbon atoms or that it is a part of the ring itself, otherwise the compound would have been desulphurized. The monothioureide of nitromalonic aldehyde was readily desulphurized when subjected to this treatment showing that the

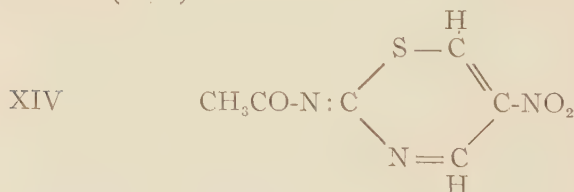
sulphur atom has altogether a different relation in its molecule than it has in the molecule of this body obtained from the piperidine condensation.

It thus appears that the free aldehyde has not condensed with the imino group. The remaining possibility is the condensation of the aldehyde with the mercapto group in the presence of piperidine, to give a β -nitro- μ -iminometathiazine (XIII). (We have since made this condensation by the use of sodium ethylate.) This would leave a free imino group, the presence of which could be proved by characteristic reactions:

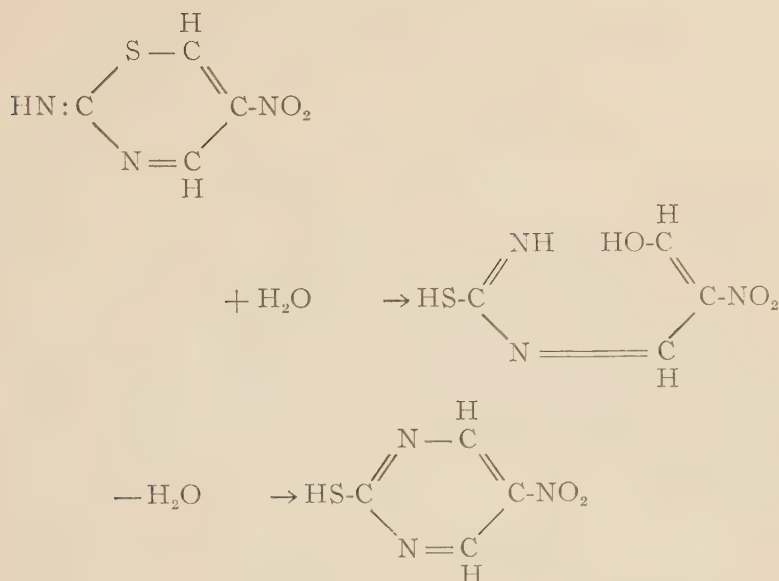


An oily mass was formed on the addition of benzene sulpho-chloride. (Hinsberg's Test.) This is proof of the presence of the imino group.

As an acetyl derivative should be possible, the body was suspended in acetic anhydride and anhydrous sodium acetate added. After warming the clear solution for a short time, and then pouring it into water, an oily mass appeared, which, upon stirring, changes in a little while to a crystalline body. Analysis gave the theoretical amount of nitrogen for β -nitro- μ -acetylminomethiazine (XIV).



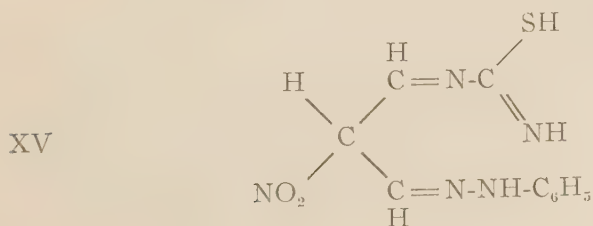
This thiazine, when warmed with either concentrated or diluted hydrochloric acid upon the steam bath for twenty hours goes into solution but is not decomposed. The original body was recovered. It was then heated at a temperature of 110° with the same result as before. It was thought the pyrimidine might be formed by the breaking of the ring between the sulphur and the carbon of the original aldehyde group as follows:



Warmed with sodium hydroxide (5N) under a reflux condenser for twenty to twenty-four hours the thiazine went into solution. The sodium salt, thus prepared, indicated no definite compound upon analysis. Deep-seated decomposition had taken place with the formation of the original sodium nitromalonic aldehyde and thio-urea as an intermediate step in the final decomposition.

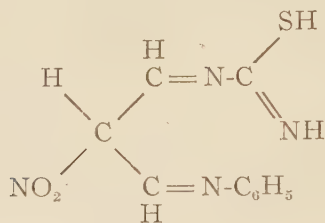
A number of derivatives of the monothioureide of nitromalonic aldehyde were made. As stated before a condensation with phenylhydrazine and aniline took place between these reagents and the free aldehyde group. The action was different in this case from that of these reagents with monoureide of nitromalonic aldehyde. The thio-urea was not displaced in this action but the following compounds, respectively, were formed:

1. Phenylhydrazone monothioureide of nitromalonic aldehyde.



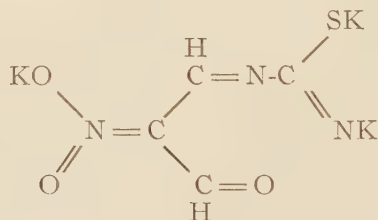
2. Anil monothioureide of nitromalonic aldehyde.

XVI



The potassium salt of the monothioureide was made and analyzed. The compound is very soluble in alkalis giving a deep red solution. The analysis for potassium gave three atoms of potassium to one molecule of the salt. The formula is probably the following:

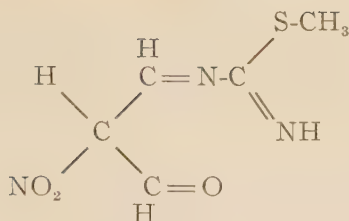
XVII



The lead salt was obtained by adding lead acetate to the sodium salt. It came down in aqueous solution with a yellowish brown color only slightly soluble in water. If this salt is warmed in aqueous solution we obtain lead sulphide which gives the characteristic galena mirror-like appearance as deposited on the sides of the vessel.

The methyl ether of this monothioureide of nitromalonic aldehyde (XVIII) was made by adding dimethylsulphate to the aqueous solution of the sodium salt. The ether came out of the solution on shaking vigorously. An attempt was made to prepare it by the method used in the formation of the β -nitro- μ -methoxypyrimidine, but without success. Only one methyl group was introduced and as there are three atoms of potassium present it is probable that the other two are not replaceable by methyl groups, owing to ready hydrolysis. The ether has a plate-like crystallization so characteristic of the sulphur compounds.

XVIII

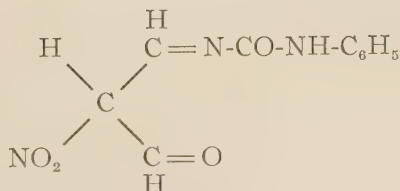


We are led, therefore, to the conclusion that this urea exists and reacts in accordance with its pseudo form. While it has not given us a pyrimidine, yet the formation of the thiazine proves beyond doubt that both the mercapto and the imino radicals are present. The mercapto with an amino group is found more reactive as a combination toward dialdehydes than is the imino with an amino group, consequently the iminothiazine must result in preference to the mercapto pyrimidine; and the diamino grouping is found still less active than the imino and amino grouping.

In order to ascertain what effect the substitution of various radicals in the amino group of urea might have upon the rate of condensation and whether these secondary amino groups would react with the aldehyde groups of nitromalonic aldehyde, the condensation of a number of different derivatives of urea with nitromalonic aldehyde was attempted.

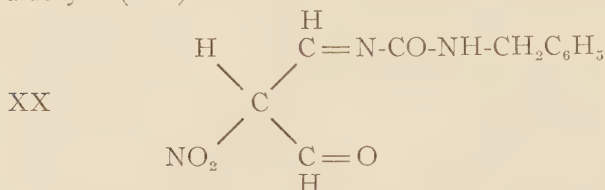
Phenylurea and nitromalonic aldehyde, when brought together in aqueous solution yielded a white, flocculent precipitate. When the mother liquor was acidified more of the same substance came out, showing that part of it existed as the sodium salt until acidified. Condensation had taken place with but one of the aldehyde groups to give a phenylureide of nitromalonic aldehyde (XIX).

XIX

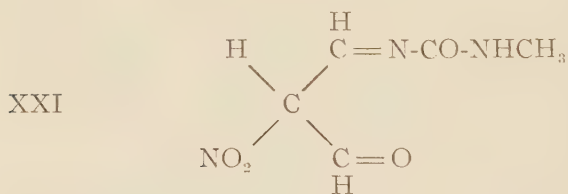


When benzyl-urea and nitromalonic aldehyde are brought together in dilute alcoholic solution a deep red color develops rapidly in the presence of piperidine, as a condensing agent. To prevent the too rapid progress of the condensation it was acidified at the end of six hours. Upon addition of dilute hydrochloric

acid the compound separated out in beautiful, lustrous, leaf-like crystals. Analysis showed that only one aldehyde group had been involved in the formation of this benzylureide of nitromalonic aldehyde (XX).



Methyl-urea also reacts readily with nitromalonic aldehyde (XXI). The solution, standing at room temperature, assumes a deep red color and at the end of twenty-four hours on the addition of acid, a light yellow, crystalline precipitate is formed in a very short time. This, like the phenyl and benzyl ureides, has included but one of the aldehyde groups in a condensation.



There was found no very distinctive difference in the rate of condensation between the aryl and the alkyl substituted ureas with nitromalonic aldehyde, so far as investigated. These secondary amino groups did not condense with an aldehyde group under the conditions tried. Methyl-urea condensed very readily and with almost quantitative yields and seemed to influence the condensation somewhat more favorably than the aryl substituted ureas.

Attempts have been made to condense urethane with nitromalonic aldehyde but so far without success. Some work has also been done on the condensation of amido compounds such as glycerine ester and analogous bodies with nitromalonic aldehyde. This work is still under progress.

EXPERIMENTAL PART

Monoureïde of Nitromalonic Aldehyde (I).



Molecular quantities of sodium nitromalonic aldehyde and urea were brought together in aqueous solution in the presence of a condensing agent, such as sodium hydroxide or piperidine. The reaction proceeded well, as was shown by the deepening of the color of the solution in the course of a few hours. After standing for one or two days at room temperature a few drops of dilute sulphuric acid (1-5) were added. At the end of ten or fifteen minutes the precipitate formed was filtered off. The mother liquor on standing gave another precipitate. The first precipitate is light yellow and only semi-crystalline, m. p. 154° (cor.). It is insoluble in chloroform, ether, benzene, carbon disulphide or carbon tetrachloride; somewhat soluble in water or acetone; readily soluble in alcohol, ethyl acetate or acetic acid.

ANALYSIS.

0.1182 gram substance gave 0.1330 gram CO_2 and 0.0423 gram H_2O .

	CALCULATED FOR	FOUND
	$\text{C}_4\text{H}_5\text{N}_3\text{O}_4$	
C	30.20	30.64
H	3.17	4.00

Sodium Salt of the Monoureïde of Nitromalonic Aldehyde (V).



In order to make the sodium salt of the monoureïde, sodium alcoholate was added to an alcoholic solution of the monoureïde. It came out as a yellowish-brown precipitate only slightly soluble in alcohol but readily soluble in water. The salt explodes feebly when warmed over a flame. The salt was recrystallized from dilute alcohol. Its three molecules of water are lost on standing over sulphuric acid.

ANALYSIS.

I. 0.2220 gram salt lost 0.0507 gram H_2O over sulphuric acid.

II. 0.1810 gram salt lost 0.0432 gram H_2O over sulphuric acid.

CALCULATED FOR		FOUND	
$\text{NaC}_4\text{H}_4\text{N}_3\text{O}_4 \cdot 3\text{H}_2\text{O}$		I.	II.
H_2O	22.97	22.84	23.87

I. 0.2220 gram salt gave 0.0744 gram Na_2SO_4 .

II. 0.3071 gram salt gave 0.0886 gram Na_2SO_4 .

CALCULATED FOR		FOUND	
$\text{NaC}_4\text{H}_4\text{N}_3\text{O}_3 \cdot 3\text{H}_2\text{O}$		I.	II.
Na	9.77	10.86	9.61

Monanil Monoureide of Nitromalonic Aldehyde (IV).



Equimolecular weights of the monanil of nitromalonic aldehyde and urea were mixed in alcoholic solution, using piperidine as a condensing agent and allowed to stand at room temperature. After a short time a yellow precipitate melting at 92° was formed. This was the dianil of nitromalonic aldehyde described by Hill and Torrey.¹⁵ When the monoureide and aniline in alcoholic solution were warmed on the steam bath to about 60° , a yellow compound melting at 146° was formed. This was the monanil of nitromalonic aldehyde¹⁶ described by these authors. When equimolecular quantities of the monanil and urea were dissolved in alcoholic solution and dry hydrogen chloride gas passed into the solution, to point of saturation, upon cooling, a precipitate of red, glistening, needle-like crystals made its appearance. These crystals are readily soluble in chloroform, acetone or benzene; slightly soluble in alcohol, carbon tetrachloride, water, or ethyl acetate; insoluble in ether or ligroin. They were recrystallized from the alcohol. The m. p. is 211.3° (cor.).

0.1752 gram of substance gave 0.3260 gram CO_2 and 0.0720 gram H_2O .

CALCULATED FOR		FOUND
$\text{C}_{10}\text{H}_9\text{N}_4\text{O}_3$		
C	51.29	51.93
H	4.27	4.70

¹⁵ Amer. Chem. Jour., 22, 100 (1899).

¹⁶ Amer. Chem. Jour., 22, 99 (1899).

The Monoxime Monoureide of Nitromalonic Aldehyde (III).



The addition of sodium hydroxide to equimolecular quantities of the monoureide and hydroxylamine hydrochloride in aqueous solution gave a yellow, leaf-like, crystalline precipitate upon standing. This product is somewhat soluble in alcohol, acetone, ethyl acetate or acetic acid; insoluble in chloroform, ether, benzene or ligroin. It was recrystallized from alcohol. The m. p. is 174.5° (cor.).

ANALYSIS.

0.1331 gram substance gave 0.1344 gram CO_2 and 0.0490 gram H_2O .

	CALCULATED FOR	FOUND
	$\text{C}_4\text{H}_6\text{N}_4\text{O}_4$	
C	27.58	27.52
H	3.44	4.11

1-Phenyl-4-Nitropyrazole. $\text{C}_8\text{H}_7\text{N}_3\text{O}_2(\text{C}_6\text{H}_5)$

In the attempt to form the phenylhydrazone monoureide of nitromalonic aldehyde, urea was always split off with the formation of the pyrazole. To an alcoholic solution of the monoureide a slight excess of phenylhydrazine acetate was added. On warming the solution and allowing it to stand, a yellowish-brown, needle-like precipitate was formed. It is insoluble in water; soluble in alcohol. This same compound was formed when the solution was not warmed thus showing that phenylhydrazone monoureide of nitromalonic aldehyde is very unstable. When recrystallized from alcohol its m. p. is 128° (uncor.).

ANALYSIS.

0.1822 gram of substance gave 0.3790 gram CO_2 and 0.0650 gram H_2O . 0.1462 gram substance gave 29.8 c.c. moist nitrogen at 23° and 717 m.m. pressure.

	CALCULATED FOR	FOUND
	$\text{C}_{10}\text{H}_7\text{N}_5\text{O}_2$	
C	57.15	56.71
H	3.70	3.99
N	22.26	22.18

Determination of Urea in Monoureide of Nitromalonic Aldehyde.

The determination was carried out according to the method of Liebig. This method consists in the titration of the urea in neutral solution with mercuric nitrate. The mercuric nitrate was so made up that 1 c.c. of solution was equal to .07 gram of HgO and about equivalent to 0.01 gram of urea. The urea was set free by adding the theoretical amount of aniline to the alcoholic solution of the monoureide.

ANALYSIS.

0.300 gram substance required 10.53 c.c. $\text{Hg}(\text{NO}_3)_2$.

CALCULATED FOR		FOUND
$\text{C}_4\text{H}_5\text{N}_3\text{O}_4$		
Urea	36.47	35.10

β -Nitro- μ -Hydroxypyrimidine (II). $\text{C}_4\text{H}_3\text{N}_2\text{O}_3$. By allowing the mother liquor, after filtering off the monoureide of nitromalonic aldehyde, to stand, there appeared a second precipitate in the course of a few hours. A continuous production of this precipitate usually extended over several days. It appears in plate-like form, somewhat deeper in color than the monoureide, insoluble in water, carbon disulphide, ether, chloroform, carbon tetrachloride, ligroin or benzene; slightly soluble in acetone, ethyl acetate or alcohol; difficultly soluble in acetic acid or acetic anhydride. When recrystallized from glacial acetic acid a m. p. of 203.5° (cor.) was obtained.

ANALYSIS.

0.1065 gram substance gave 28.5 c.c. moist nitrogen at 20° and a pressure of 721.4 m.m.

CALCULATED FOR		FOUND
$\text{C}_4\text{H}_3\text{N}_2\text{O}_3$		
N	29.79	29.69

The percentage yields of the monoureide and the pyrimidine from 0.8 gram sodium nitromalonic aldehyde and 0.3 gram urea, are given below. These yields are based upon the theoretical weight of the substances possible from 0.8 gram of sodium nitromalonic aldehyde.

MONOUREÏDE	YIELD	PYRIMIDINE	YIELD	TOTAL YIELD
0.480 gram	59.40%	0.1243 gram	17.31%	76.71%
0.513 gram	63.49%	0.1143 gram	15.92%	79.41%
0.539 gram	66.71%	0.0900 gram	12.53%	79.10%
0.542 gram	67.08%	0.0844 gram	11.75%	78.83%

These figures were chosen from some of the best results. Many of the condensations gave very much smaller yields. As can be seen the yield of the pyrimidine was low when the weight of monoureide was high, and vice versa.

Attempts to Condense the Monoureide into β -Nitro- μ -Hydroxypyrimidine.

a. The monoureide was dissolved in acetic anhydride and treated with dry hydrogen chloride. A light yellow precipitate formed on cooling, having the properties of the pyrimidine, m. p. 203° (uncor.). The compound was the pyrimidine but the yield was only fifteen to twenty-five per cent. of the theoretical.

b. About 0.2 gram of the monoureide was placed in 15 c.c. of water and four drops of concentrated sulphuric acid added. The solution warmed at 60° - 65° on the steam bath became deep red and on cooling a yellow precipitate appeared, m. p. 194° (uncor.). The m. p. is low because there is still probably some monoureide present.

c. When dilute sulphuric is added to the urea-nitromalonic aldehyde reaction mixture, which is at a temperature of about 50° , most of the precipitate comes out as the pyrimidine. Care must be taken to avoid decomposition from having the solution too warm. This method was not uniformly satisfactory.

d. On allowing the monoureide to remain in the mother-liquor at room temperature after acidification, a large part of it is further condensed to the pyrimidine.

SAMPLE I.

TIME	M. P.
1 hour	156°
2 days	188°
3 days	192°

SAMPLES II AND III.

TIME	M. P. II	M. P. III
2 days	133°	142°
4 days	140°	155°
8 days	164°	161°

No further heightening of m. p. As can be seen, the above process could not be depended upon for production of the pyrimidine.

e. 0.200 gram of the monoureide dissolved in acetic anhydride and heated in a sealed tube at 120° - 140° for twelve hours gave only decomposition products.

f. When heated with diluted hydrochloric acid and also with sulphuric acid in a sealed tube at 100° – 110° , the monoureide underwent a decomposition in each case with the formation of ammonium chloride and ammonium sulphate, respectively.

g. The monoureide, heated on the steam bath under a reflux condenser with acetic anhydride for four hours, went into solution. On cooling, a nearly colorless compound formed with a melting point at 176° (uncor.). This experiment was repeated, the warming continued for a longer time, but with no better success. Attempts were made to dehydrate the monoureide and form the pyrimidine by dissolving the monoureide in acetic anhydride and adding such dehydrating agent as zinc chloride, anhydrous sodium acetate, phosphorus pentoxide or concentrated sulphuric acid, but these were without positive results.

h. The sodium salt of the pyrimidine can be made by warming the monoureide with sodium ethylate in absolute alcohol under a reflux condenser for several hours. The salt of the pyrimidine is less soluble in alcohol than that of monoureide, consequently it separates as fast as formed. The sodium salts can be distinguished by their different solubilities in absolute alcohol, as stated above, and the color of their aqueous solutions. The salt of the pyrimidine gives a deep red aqueous solution while that of the monoureide is yellow in color. The largest yields of the salt were about 10% of theory.

None of the dehydrating methods described above could be depended upon for satisfactory yields. Most of the β -nitro- μ -hydroxypyrimidine used in this research was obtained by allowing the mother liquor from the monoureide to stand for a time after filtering from the monoureide.

Potassium Salt of β -Nitro- μ -Hydroxypyrimidine (VI).



This salt was made by adding potassium hydroxide to the pyrimidine. The solution became deep red on addition of the hydroxide. It is slightly soluble in alcohol but readily soluble in water.

ANALYSIS.

0.1846 gram air dried salt lost 0.0166 gram H_2O over sulphuric acid.

CALCULATED FOR		FOUND
$\text{KC}_4\text{H}_2\text{N}_3\text{O}_2\cdot\text{H}_2\text{O}$		
H_2O	9.14	8.99

0.1846 gram salt gave 0.0806 gram K_2SO_4 .

	CALCULATED FOR	FOUND
	$KC_4H_2N_3O_2 \cdot 4H_2O$	
K	19.80	19.60

Barium Salt of β -Nitro- μ -Hydroxypyrimidine.



The barium salt was made by addition of barium hydroxide to a solution of the ammonium salt formed by dissolving the pyrimidine in ammonium hydroxide. It gave a reddish brown precipitate only slightly soluble in water. The salt becomes darker when the water of crystallization is driven off. Heated to a temperature of 110° it loses its water of crystallization.

ANALYSIS.

0.1776 gram salt lost 0.0236 gram H_2O at a temperature of 110° .

	CALCULATED FOR	FOUND
	$BaC_8H_4N_6O_6 \cdot 4H_2O$	
H_2O	14.73	13.30

0.1776 gram salt gave 0.07295 gram $BaSO_4$.

	CALCULATED FOR	FOUND
	$BaC_8H_4N_6O_6 \cdot 4H_2O$	
Ba	24.08	24.04

Silver Salt of β -Nitro- μ -Hydroxypyrimidine.



This silver salt was prepared by adding silver nitrate to the aqueous solution of the ammonium salt. It is reddish yellow and only slightly soluble in water.

ANALYSIS.

0.1170 gram salt gave 0.0504 gram Ag.

	CALCULATED FOR	FOUND
	$AgC_4H_2N_3O_2$	
	43.55	43.10

Methyl Ether of β -Nitro- μ -Hydroxypyrimidine (VII).



The dry sodium salt of the pyrimidine, prepared as previously described, was suspended in absolute alcohol and methyl iodide

added. This mixture was warmed on the steam bath under a reflux condenser for three hours, then it was carefully evaporated to dryness and the residue extracted with benzene. The ether is a colorless, plate-like, crystalline compound, readily soluble in benzene; somewhat soluble in alcohol or water; insoluble in ether. Yields were very poor. After recrystallization from benzene it melted at 167.5° (uncor.). When heated to 167.5° or slightly above and let cool and then again warmed to 167.5° , the compound melted sharply showing it to be stable, *i. e.*, the methoxyl group has not wandered to a new position. Final purification gave the m. p. 168.9° (cor.).

ANALYSIS.

0.1210 gram ether gave 0.1724 gram CO_2 and 0.0378 gram H_2O .

	CALCULATED FOR	FOUND
	$\text{C}_5\text{H}_5\text{N}_3\text{O}_3$	
C	38.69	38.86
H	3.25	3.49

To determine the position of the methoxyl group in the ring an analysis and estimation of this group was carried out according to the method of Zeisel. The ether was placed in a small flask in which was placed a solution of hydriodic acid and ammonium iodide. This flask led to another in which was a solution of hydriodic acid alone, next to a flask containing water, which would wash the gas free of hydriodic acid, then to a condenser inclined toward the wash bottle and kept at a temperature of 60° . Finally through another wash flask containing water and red phosphorus and then to the flasks containing silver nitrate in a solution of dilute alcohol. Here the methyl iodide, formed in the first flask, was precipitated as silver iodide. It has been found that methoxyl groups attached to a carbon atom split off at a much lower temperature (40° - 80° , usually) than those attached to a nitrogen atom. This methoxyl group was split off at a temperature of 40° thus proving it to be attached to the carbon atom.

ANALYSIS.

0.1530 gram ether gave 0.1906 gram AgI .

	CALCULATED FOR	FOUND
	$\text{C}_5\text{H}_5\text{N}_3\text{O}_3$	
CH_3	9.68	7.99

Attempts were made to reduce the nitropyrimidine and form the amino-pyrimidine but without success. Decomposition always took place simultaneously with the reduction and no definite compound could be isolated.

β -Nitro- μ -Phenylpyrimidine (VIII). $C_4H_2N_3O_3(C_6H_5)$. This pyrimidine was made by mixing equimolecular quantities of benzamidine hydrochloride and sodium nitromalonic aldehyde in aqueous solution. In the absence of a condensing agent a white, flocculent precipitate formed almost immediately. When sodium hydroxide was used for condensation, the precipitate did not form so completely until the excess of sodium hydroxide was neutralized. The compound is somewhat soluble in alcohol, ether or benzene; insoluble in water. It gave no test for sodium salt before acidifying, consequently the sodium salt of the intermediate body first formed, must have been hydrolyzed. The sodium salt cannot be made by warming this substance with sodium hydroxide in aqueous solution or with sodium ethylate in alcoholic solution, consequently no replaceable hydrogen can be present. Recrystallized from alcohol and ether solution the m. p. is 219° (cor.).

ANALYSIS.

0.1312 gram gave 0.2894 gram CO_2 and 0.0444 gram H_2O .
0.1472 gram gave 28.20 c.c. moist nitrogen at 22° and 714 m.m. pressure.

	CALCULATED FOR	FOUND
	$C_{10}H_7N_3O_2$	
C	60.00	60.17
H	3.51	3.78
N	20.89	20.82

β -Nitro- μ -Aminopyrimidine (IX). $C_4H_2N_3O_2(NH_2)$. When equimolecular quantities of guanidine carbonate and sodium nitromalonic aldehyde are brought together in an aqueous solution, a precipitate is formed almost immediately in the absence of a condensing agent. The yield is greatly increased by addition of piperidine as a condensing agent. The compound is soluble in dilute hydrochloric acid, acetone, alcohol, ethyl acetate or sodium hydroxide; somewhat soluble in water; insoluble in ether, ligroin, chloroform, carbon tetrachloride, or benzene. It was recrystallized from alcohol, giving colorless, needle-like crystals melting at 236° (cor.).

ANALYSIS.

0.1828 gram substance gave 0.2280 gram CO_2 and 0.0424 gram H_2O .

	CALCULATED FOR	FOUND
	$\text{C}_4\text{H}_4\text{N}_4\text{O}_2$	
C	34.28	34.00
H	2.86	2.59

Silver Salt of β -Nitro- μ -Hydroxypyrimidine.



When this pyrimidine is boiled with alkali, ammonia is given off. The silver salt was prepared by warming the pyrimidine with concentrated ammonium hydroxide until the odor of ammonia was no longer to be detected and the solution had become a deep red and then adding silver nitrate. The salt is reddish-brown, almost insoluble in water and resembles the silver salt of the β -nitro- μ -hydroxypyrimidine already described. The following analyses serve also to establish the identity of these two silver salts.

ANALYSIS.

0.1788 gram substance gave 27.10 c.c. moist nitrogen at 23° and 720 m.m. pressure.

	CALCULATED FOR	FOUND
	$\text{AgC}_4\text{H}_2\text{N}_3\text{O}_2$	
N	16.93	16.60

I. 0.1040 gam substance gave 0.0430 gram Ag.

II. 0.1430 gram substance gave 0.0620 gram Ag.

	CALCULATED FOR	FOUND
	$\text{AgC}_4\text{H}_2\text{N}_3\text{O}_3$	I. II.
Ag	43.55	41.35 43.36

When this silver salt is treated with hydrochloric acid and the clear solution, freed of silver chloride, is evaporated to small bulk, the yellow, plate-like, semicrystalline hydroxypyrimidine is obtained. The methyl-ether of this compound was made by warming the silver salt with methyl iodide in methyl alcohol under a reflux condenser for two hours. We were able to isolate a small amount of the ether which gave all the reactions characteristic of this compound as prepared originally from hydroxypyrimidine itself.

Presence of the Amino Group in β -Nitro- μ -Aminopyrimidine.

Hoffman's Test.

a. An alcoholic solution of the aminopyrimidine was warmed with alcoholic potash. It gave the characteristic odor of a carbylamine.

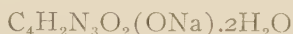
Hinsberg's Test.

When the compound was warmed with benzenesulphochloride a clear solution was obtained.

Liebermann's Nitrosamine Test.

On adding sodium nitrite to an acid solution of this pyrimidine no oily product was obtained as would have occurred had an imino group been present. These tests prove the presence of the amino group and absence of the imino.

Sodium Salt of β -Nitro- μ -Hydroxypyrimidine (VI).



This sodium salt was prepared by warming the aminopyrimidine with a very slight excess of approximately normal sodium hydroxide until the odor of ammonia was no longer noticeable. The solution was then evaporated to small bulk with very great care, lest decomposition occur in the presence of the alkali, after which it was allowed to stand until the salt crystallized out. The salt is a reddish-brown. It is slightly soluble in alcohol but readily soluble in water giving a deep red color to the solution.

ANALYSIS.

0.1908 gram salt gave .0342 gram H_2O .

CALCULATED FOR		FOUND
$\text{NaC}_4\text{H}_2\text{N}_3\text{O}_3.2\text{H}_2\text{O}$		
H_2O	18.59	17.82

0.1908 gram salt gave 0.0708 gram Na_2SO_4 .

CALCULATED FOR		FOUND
$\text{NaC}_4\text{H}_2\text{N}_3\text{O}_3.2\text{H}_2\text{O}$		
Na	11.56	12.38

β -Nitro- μ -Acetylaminopyrimidine (X).



The acetyl derivative of the aminopyrimidine was prepared by warming this compound with an excess of acetic anhydride in the presence of a small amount of anhydrous sodium acetate. The

solution was heated under a reflux condenser on the steam bath for about three hours. When the solution was allowed to cool, the acetyl compound separated out in beautiful, colorless, long, needle-like crystals. The yield is about 80% of the theoretical. The compound is readily soluble in acetic acid, benzene, alcohol or chloroform; slightly soluble in water, carbon tetrachloride, ethyl acetate, or acetone; insoluble in ether or ligroin. When recrystallized from alcohol it has a m. p. of 172.5° (cor.).

NITROGEN DETERMINATION.

0.1238 gram substance gave 34.5 c.c. moist nitrogen at 27° and 709 m.m. pressure.

CALCULATED FOR		FOUND
	$C_9H_6N_4O_3$	
N	30.86	30.84

Symmetrical β,β' -Dinitro- μ,μ' -Dipyrimidyl Thiourea (XI).



This substance is readily prepared by suspending the aminopyrimidine in carbon disulphide and adding a small amount of potassium hydroxide to the mixture kept for a short time at 60° . The pyrimidine appeared as an oily, yellow mass in the bottom of the vessel. After decanting the excess of carbon disulphide and digesting the mass with alcohol the oil soon passed over to a glistening, plate-like, crystalline substance with the characteristic appearance of so many of the thio compounds. It is soluble in alcohol, carbon disulphide or ethylacetate; somewhat soluble in water or ether; slightly soluble in acetone, chloroform, or benzene; insoluble in ligroin or carbon tetrachloride. When recrystallized from alcohol it has a m. p. of $230-1^{\circ}$ (cor.).

NITROGEN DETERMINATION.

0.1005 gram gave 32 c.c. of moist nitrogen at 23° and 716 m.m. pressure.

CALCULATED FOR		FOUND
N	34.78	34.36

Attempts to reduce this pyrimidine and isolate the p-amino-pyrimidine were unsuccessful. Tin and hydrochloric acid, zinc and hydrochloric acid, zinc and acetic acid, stannous chloride in acid

solution and hydrogen sulphide in alkaline solution were all tried but in each case decomposition took place simultaneously with the reduction.

Monothioureide of Nitromalonic Aldehyde (XII).



Molecular quantities of thio-urea and nitromalonic aldehyde in aqueous solution react very quickly in the presence of a condensing agent. The color of the solution becomes a deep red and in the course of fifteen or twenty minutes a light yellow, needle-like, finely crystalline precipitate is formed. This precipitate is the thiazine described later. On addition of a few drops of dilute acid to the solution, freed from the thiazine, the monothioureide of nitromalonic aldehyde is thrown down. This compound is a yellow, semicrystalline substance, soluble in acetic acid; slightly soluble in alcohol, acetone or ethyl acetate; insoluble in water, benzene, carbon disulphide, ether or ligroin. This compound was desulphurized by warming the alkaline solution with either lead acetate or mercuric oxide. When recrystallized from acetic acid it had a m. p. of 206.5° (cor.). The same body was obtained by adding dilute acid to the solutions in which sodium hydroxide or diethylamine was used as the condensing agent. In these cases the thiazine was not formed.

ANALYSIS.

0.1400 gram substance gave 0.1420 gram CO_2 and 0.0441 H_2O .

0.0776 gram substance gave 17.22 c.c. nitrogen at 23° and 740 m.m. pressure.

	CALCULATED FOR	FOUND
	$\text{C}_4\text{H}_3\text{N}_3\text{SO}_3$	
C	27.45	27.66
H	2.86	3.50
N	24.00	24.11

Determination of Sulphur by use of Sodium Peroxide and Estimation as Barium Sulphate.

- I. 0.1740 gram substance gave 0.2214 gram BaSO_4 .
- II. 0.1648 gram substance gave 0.2298 gram BaSO_4 .
- III. 0.3112 gram substance gave 0.4094 gram BaSO_4 .

	CALCULATED FOR	FOUND		
	$\text{C}_4\text{H}_5\text{N}_3\text{SO}_3$	I	II	III
S	18.30	17.50	19.50	18.06

Preparation of the Salts of Monothioureide of Nitromalonic Aldehyde.

Potassium Salt of Monothioureide of Nitromalonic Aldehyde (XVII). $K_3C_4H_2N_3SO_3$.

The potassium salt was made by adding dilute potassium hydroxide to the compound suspended in water. It immediately went into solution giving a deep red color to this solution. On careful evaporation to small bulk and allowing to stand the salt crystallized out in long, flat, reddish-brown crystals. The air-dried salt has no water of crystallization.

ANALYSIS.

- I. 0.3090 gram salt gave 0.2815 gram K_2SO_4 .
- II. 0.1208 gram salt gave 0.1154 gram K_2SO_4 .
- III. 0.5834 gram salt gave 0.5474 gram K_2SO_4 .

	CALCULATED FOR		FOUND		
	$K_3C_4H_2N_3SO_3$		I	II	III
K	40.63		40.80	42.78	42.00

Methyl Ether of the Monothioureide of Nitromalonic Aldehyde (XVIII). $C_4H_1N_3O_2(SCH_3)$.

It was thought this ether might be prepared in accordance with the method employed for the preparation of the ether of the hydroxypyrimidine, *i. e.*, by warming the sodium salt with methyl iodide, but this procedure met with no success. It was therefore prepared by adding dimethyl sulphate to the aqueous solution of the sodium salt. On shaking, the ether separated out. It is a yellow, plate-like, crystalline compound; soluble in benzene, ether or alcohol; insoluble in water. This ether is fairly stable since it again melts at 78° (uncor.) after having been warmed above this temperature. The odor of the thio compound is very evident when the ether is warmed, or on long standing in a dessicator. Recrystallized from ether its m. p. is $78-9^\circ$ (cor.).

NITROGEN DETERMINATION.

0.0648 gram substance gave 14.05 c.c. moist nitrogen at 24° and 720 m.m. pressure.

	CALCULATED FOR		FOUND	
	$C_3H_7N_3SO_3$			
N	22.30		23.50	

The aldehyde group reacted with phenylhydrazine and with aniline to form a hydrazone and an anil, respectively. Thiourea

was not split off in this case as was urea when the monoureide of nitromalonic aldehyde was treated in a similar manner.

β -Nitro- μ -Iminometathiazine (XIII). $C_4H_3N_3SO_2$. This compound is always formed when piperidine is used as the condensing agent in the solution of nitromalonic aldehyde and thio-urea. It may also be made by the action of sodium ethylate on the monothioureide. When the thioureide is suspended in cold alcohol and piperidine added with shaking, the solution reddens and the monothioureide goes into solution with the immediate precipitation of the thiazine. This thiazine is a very stable compound, not being broken up by acids nor by alkalis except on long warming. It is not desulphurized by boiling an alkaline solution with lead acetate nor with mercuric oxide, thus indicating that the sulphur atom is placed between two carbon atoms. There was no reaction with phenylhydrazine nor with aniline, which proves the absence, in a negative way, of the aldehyde group. It gave a yellow, oily mass when the alkaline solution was heated with benzene sulphochloride. This indicates the presence of an imino group. The thiazine is soluble in acetone or benzene; fairly soluble in alcohol, acetic acid or ethyl acetate; somewhat soluble in water.

When recrystallized from alcohol it gave a m. p. of 152° (cor.).

NITROGEN DETERMINATION.

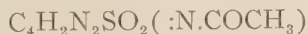
I. 0.1932 gram substance gave 46 c.c. moist nitrogen at 21° and 720.5 m.m. pressure.

II. 0.1204 gram substance gave 29.94 c.c. moist nitrogen at 22.5° and 718.5 m.m. pressure.

III. 0.1383 gram substance gave 34.68 c.c. moist nitrogen at 25° and 715 m.m. pressure.

	CALCULATED FOR	FOUND		
	$C_4H_3N_3SO_2$	I	II	III
N	26.87	26.20	27.15	27.00

β -Nitro- μ -Acetylminometathiazine (XIV).



This derivative was prepared by warming the thiazine with an excess of acetic anhydride for an hour at a temperature of 50° . The solution was then poured into water. The oil, first separating out, gradually hardened to a crystalline, needle mass, light yellow in color. The acetyl compound was hydrolyzed to the original thiazine by warming the acidified solution. It is readily sol-

uble in alcohol, acetone, benzene, ethyl acetate or carbon tetrachloride; somewhat soluble in ligroin or acetic acid; slightly soluble in water; insoluble in ether. When recrystallized from alcohol the m. p. is $141-2^{\circ}$ (cor.).

NITROGEN DETERMINATION.

0.1265 gram substance gave 26 c.c. moist nitrogen at 25° and 708 m.m. pressure.

	CALCULATED FOR	FOUND
	$C_6H_5N_3SO_3$	
N	21.16	21.89

Monophenylureide of Nitromalonic Aldehyde (XIX).



Equimolecular quantities of nitromalonic aldehyde and phenylurea were dissolved in dilute alcohol and a few drops of piperidine added. From the deeply colored solution a flocculent precipitate was soon thrown down. It is soluble in alcohol or ether but insoluble in water. When recrystallized from alcohol it gave a m. p. of $176-7^{\circ}$ (cor.).

ANALYSIS.

0.1504 gram substance gave 0.2746 gram CO_2 and 0.0552 gram H_2O .

	CALCULATED FOR	FOUND
	$C_{10}H_5N_3O_4$	
C	51.06	49.80
H	3.86	4.10

Monobenzylureide of Nitromalonic Aldehyde (XX).



Benzylurea and nitromalonic aldehyde condense very readily when brought together in equimolecular quantities in dilute alcoholic solution. The solution darkened so rapidly that at the end of six hours it was acidified to prevent decomposition. The precipitate came down almost immediately and in a good yield, appearing in plate-like, colorless crystals. It is soluble in alcohol, chloroform, acetone or ethyl acetate; insoluble in benzene, carbon tetrachloride or ligroin. When recrystallized from alcohol it gave a m. p. of $150-2^{\circ}$ (cor.).

NITROGEN DETERMINATION.

0.1950 gram substance gave 28.8 c.c. moist nitrogen at 23° and 722 m.m. pressure.

	CALCULATED FOR	FOUND
	$C_{11}H_{11}N_3O_4$	
N	16.86	16.18

Monomethylureide of Nitromalonic Aldehyde (XXI).



This compound can be prepared by introducing equimolecular quantities of methylurea and nitromalonic aldehyde in aqueous solution in the presence of a few drops of piperidine. The solution becomes a deep red at the end of one day. Dilute acid is added and a yellow, crystalline precipitate appears almost immediately. It is soluble in alcohol or acetone; somewhat soluble in chloroform, ethyl acetate, or ligroin; insoluble in ether, benzene or carbon tetrachloride. Recrystallized from alcohol it has a m. p. of 186-7° (cor.).

ANALYSIS.

0.2076 gram substance gave 0.2652 gram CO_2 and 0.0720 gram H_2O .

	CALCULATED FOR	FOUND
	$C_5H_7N_3O_4$	
C	34.64	34.84
H	4.04	3.88

SUMMARY

We have shown by this research that the amino groups of certain α -diamino compounds may be made to react with the aldehyde groups of nitromalonic aldehyde with the formation of pyrimidine bodies; that the amino-imino grouping in guanidine or benzamidine is a more reactive combination than the diamino grouping in urea or guanidine; that thiourea exists and reacts in the pseudo-form with nitromalonic aldehyde; and finally that the secondary amino group in the presence of the primary amino group does not react with nitromalonic aldehyde.

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